



## King's Research Portal

DOI:

[10.1016/j.jclinepi.2018.04.017](https://doi.org/10.1016/j.jclinepi.2018.04.017)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

N. Papageorgiou, S., Xavier, G. M., Cobourne, M. T., & Eliades, T. (2018). Registered trials report less beneficial treatment effects than unregistered ones: A meta-epidemiological study in orthodontics. *Journal of Clinical Epidemiology*. <https://doi.org/10.1016/j.jclinepi.2018.04.017>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

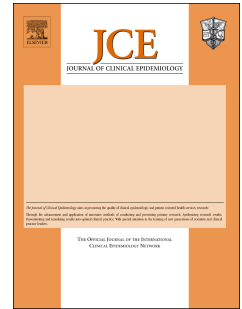
### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

# Accepted Manuscript

Registered trials report less beneficial treatment effects than unregistered ones: a meta-epidemiological study in orthodontics

Spyridon N. Papageorgiou, Guilherme M. Xavier, Martyn T. Cobourne, Theodore Eliades



PII: S0895-4356(17)31138-1

DOI: [10.1016/j.jclinepi.2018.04.017](https://doi.org/10.1016/j.jclinepi.2018.04.017)

Reference: JCE 9644

To appear in: *Journal of Clinical Epidemiology*

Received Date: 4 October 2017

Revised Date: 6 April 2018

Accepted Date: 20 April 2018

Please cite this article as: Papageorgiou SN, Xavier GM, Cobourne MT, Eliades T, Registered trials report less beneficial treatment effects than unregistered ones: a meta-epidemiological study in orthodontics, *Journal of Clinical Epidemiology* (2018), doi: 10.1016/j.jclinepi.2018.04.017.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Registered trials report less beneficial treatment effects than unregistered ones: a meta-epidemiological study in orthodontics**

Spyridon N. Papageorgiou<sup>a,\*</sup>, Guilherme M. Xavier<sup>b</sup>, Martyn T. Cobourne<sup>b</sup>, Theodore Eliades<sup>a</sup>

*<sup>a</sup>Clinic of Orthodontics and Pediatric Dentistry, Center of Dental Medicine, University of Zurich,  
Plattenstrasse 11, Zurich 8032, Switzerland*

*<sup>b</sup>Department of Orthodontics, King's College London Dental Institute, London SE1 9RT, United Kingdom*

Running title: Trial registration and bias

\*Corresponding author: snpapage@gmail.com.

Words in abstract: 200

Words in text: 2952

Registration: PROSPERO (CRD42017072043)

## Abstract

**Objectives:** Clinical trial registration is widely recommended, since it allows tracking of trials that helps ensure full and unbiased reporting of their results. Aim of the present overview was to provide empirical evidence on bias associated with trial registration via a meta-epidemiological approach.

**Study Design and Settings:** Six databases were searched in September 2017 for randomized clinical trials and systematic reviews thereof assessing the effects of orthodontic clinical interventions. After duplicate study selection and data extraction, statistical analysis included a two-step meta-epidemiological approach within- and across-included meta-analyses with a Paule-Mandel random-effects model to calculate Differences in Standardized Mean Differences ( $\Delta$ SMD) between registered and unregistered trials and their 95% Confidence Intervals (CI), followed by subgroup and sensitivity analyses.

**Results:** A total of 16 meta-analyses with 83 trials and 4988 patients collectively were finally included, which indicated that registered trials reported less beneficial treatment effects than unregistered trials ( $\Delta$ SMD=-0.36; 95% CI=-0.60,-0.12). Although some small-study effects were identified, sensitivity analyses according to precision and risk of bias indicated robustness.

**Conclusions:** Signs of bias from lack of trial protocol registration were found with non-registered trials reporting more beneficial intervention effects than registered ones. Caution is warranted by the interpretation of non-registered randomized trials or systematic reviews thereof.

**Keywords:** Randomized clinical trials; Protocol registration; Empirical bias; Meta-analysis; Meta-epidemiology

## Manuscript

### 1. Introduction

#### 1.1. Background

Randomized clinical trials are regarded as the gold standard in comparative efficacy research and form the basis for translating research evidence to clinical practice [1]. Among their advantages, methodological transparency is crucial and entails registration of the trial design protocol in a public domain prior to trial initiation in order to improve accountability in the conduct and reporting of research [2]. Trial protocols can be used post hoc to compare the original plan with subsequent procedures and analyses [3], thereby potentially reducing the risk of data dredging. *A priori* trial registration can additionally safeguard against bias-related phenomena such as delayed publication or non-publication of trials, selective reporting of outcomes, manipulation of the analysis plan, and counting covert duplicate publications within systematic reviews as separate trials [3-6].

Insights on trial characteristics systematically associated with treatment effects can be gleaned through meta-epidemiological studies. This is a subgenre of the big family of overviews of reviews, wherein data from a collection of meta-analyses is integrated and classified according to a specific study-level trait in order to empirically assess its influence on treatment effects [7].

A recent comprehensive meta-epidemiological study reported that non-registered or retrospectively registered trials tend to show larger treatment effects [8]. Although the effect was not statistically significant, this is confirmed by cross-sectional overviews of randomized trials in cardiology [9] or general medicine [10] that report weak associations between positive findings and trial registration, although the effects were not always consistent. It is also important to note that these analyses were based on qualitative evaluations of trial results by using either a P value cut-off or the trialists' interpretation of the results in text, both of which can be problematic.

#### 1.2. Scope

The aim of this meta-epidemiological study is to provide empirical evidence of possible differences in the results of registered and non-registered randomized clinical trials in orthodontics as a sign of bias, including its direction and magnitude.

## 2. Methods

### 2.1. Protocol, eligibility criteria, and registration

The protocol for this overview of reviews and trials was made *a priori* based loosely on the format of a systematic review, registered in PROSPERO (CRD42017072043), and all *post hoc* changes to the protocol were appropriately noted. According to the criteria set *a priori*, eligibility included parallel randomized clinical trials (or meta-analyses thereof) on human patients on any experimental intervention compared to a conventional or control group with any binary/continuous outcome in orthodontics and dentofacial orthopedics. Excluded were non-clinical studies, animal studies, and non-randomized studies. Split-mouth (within-person) randomized clinical trials were excluded as the suboptimal reporting of such studies in orthodontics makes their integration in meta-epidemiological synthesis difficult [11, 12]. Additionally, only 'hard' outcomes pertaining to overall treatment success, treatment duration, or treatment adverse effects were included, because these can easily be categorized as beneficial/detrimental and are empirically more robust than surrogate outcomes [13]. Ultimately, only meta-analyses of at least three trials, including at least one registered and at least one non-registered trial were included so that meta-epidemiological effects can be estimated. This meta-epidemiological study is loosely conducted and reported according to guidelines for systematic reviews and overviews thereof [1, 7, 14].

### 2.2. Information sources and literature search

The literature search for this study was done in two steps. Initially data from a recent study [15] that searched the ClinicalTrials.gov and the ISRCTN registries were used to identify all orthodontic subjects with at least one registered randomized trial (Supplementary Table 1). Then, separate literature searches were performed for all identified subjects in order to identify eligible registered or non-registered randomized trials or systematic reviews with meta-analyses, including at least one randomized trial. A total of six electronic databases (MEDLINE through Pubmed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts of Reviews of Effects, Web of Knowledge, and Scopus) were searched systematically by one author (SNP) without any limitations from inception up to September 2<sup>nd</sup>, 2017 (Supplementary Table 2). Four additional sources (Scopus, Google Scholar, ClinicalTrials.gov, and ISRCTN registry) were manually searched for additional

trials. No limitations concerning language, publication year or status were applied. All identified relevant systematic reviews with meta-analysis were manually searched for additional trials.

### *2.3. Study selection, data collection, and risk of bias in individual studies*

The titles and abstracts of all studies identified by the literature searches were screened by one author (SNP), excluding all those obviously non-relevant according to the study scope and non-clinical studies. The remaining full texts were checked for eligibility by one author (SNP) with a subsequent duplicate independent checking in full by another author (GMX), while conflicts were resolved by the last two authors (MTC, TE). All identified randomized trials were separately checked for eligibility on study design, intervention, and outcome. All meta-analyses included in identified systematic reviews were checked for any eligible randomized trials that could be added to a single meta-analysis without overlap on each topic and outcome to inform the meta-epidemiological synthesis. Trial overlaps within each meta-analysis and across meta-analyses were removed by assigning the Pubmed unique identifier to each trial and including each trial only once per meta-analysis. Where needed, interquartile ranges were converted to standard deviations and similar measurements concerning the same outcome (like visual analogue and Likert pain scales) were combined. When subgroup analyses were performed in identified meta-analyses, these were ignored and the overall pooled estimate was used.

Characteristics of included meta-analysis and trials were extracted fully in duplicate by two authors (SNP, GMX) using pre-determined and piloted extraction forms. Extracted data included first author name, publication year, outcome measured, outcome data, and trial registration status. Registration status originated from a previous study on two trial registers [15] and was subsequently supplemented by reading the full text of the published paper. Missing data were requested by trialists or calculated from available high-quality graphs with the freely-available Web Plot Digitizer version 3.12 (<http://arohatgi.info/WebPlotDigitizer>).

The risk of bias of the included randomized trials was not planned to be comprehensively assessed with the Cochrane risk of bias tool [1], as this was outside the scope of this study. Only the adequacy of the generation of random sequence and blinding of outcome assessor was assessed independently by two authors (SNP, GMX) according to the Cochrane guidelines [1] as low or unclear/high to use this for sensitivity analyses. Differences in risk of bias between registered and non-

registered trials were gauged with cross-tabulation and calculation of relative risks and their 95% Confidence Intervals (CI).

#### 2.4. Data synthesis

As the clinical effects of orthodontic trials are bound to be influenced by appliance [16, 17], patient [18], or study design-related characteristics [6, 19, 20] a random-effects model was chosen a priori, even though no clear guidance for model choice in meta-epidemiological studies exists. The Paule-Mandel random-effects variance estimator was preferred to the DerSimonian and Laird one, following recent advice [21].

For all included meta-analyses, the Standardized Mean Difference (SMD) was chosen as the effect measure because it standardizes estimates by their variability and enables overall synthesis [22]. Binary outcomes were planned to be converted to SMDs prior to pooling, but no eligible binary outcomes were identified. All outcomes were categorized as beneficial or harmful and all SMDs were recoded on the same direction, so that a positive SMD was beneficial. When trials with more than one experimental (interventional) trial arms were included, these arms were pooled prior to the meta-analysis to avoid double-counting of control patients.

Random-effects meta-regression with the Paule-Mandel variance estimator was performed, fully incorporating heterogeneity between-trials, to derive a difference in SMDs ( $\Delta$ SMD) and the standard error within each meta-analysis, according to registration status of included trials. Ultimately, Paule-Mandel random-effects meta-analysis (i.e. meta-epidemiological synthesis) was used to pool the overall effect of trial registration across all component meta-analyses taking into account variability across them. The magnitude for SMDs and  $\Delta$ SMD was arbitrarily assessed using Cohen's [22] guidelines: up to 0.2=small effect, 0.2 to 0.5=medium effect, 0.5 to 0.8=large effect, and larger than 0.8=very large effect. These cut-off values were also adopted to visually enhance the produced forest plot [23].

Absolute and relative between-meta-analyses heterogeneity/inconsistency was quantified with the  $\tau^2$  metric and the  $I^2$  statistic, respectively. The latter is defined as the proportion of total variability in the results explained by heterogeneity, and not chance [24]. 95% CIs around all heterogeneity measures were calculated to quantify existing uncertainty [25], while 95% predictive intervals were to be calculated for the meta-epidemiological synthesis to provide a range of possible effects for a future



clinical setting [26]. All analyses were run in Stata SE 14.0 (StataCorp, College Station, TX) by one author (SNP) and all material was openly made available through Zenodo [27]. A two-tailed P-value of 0.05 was considered significant for hypothesis-testing, except for a 0.10 used for the test of heterogeneity and reporting biases, due to low power [28].

### *2.5. Additional analyses*

Random-effects subgroup analyses were planned a priori to identify possible differences in the effect of trial registration among various orthodontic topics, binary versus continuous outcomes, subjective versus objective outcomes, and positive or negative effect direction with an interaction term by Paule-Mandel meta-regression. Indications of reporting biases (including small-study effects) were assessed with Egger's linear regression test [29] and contour-enhanced funnel plots [30].

Robustness of the results to possible sources of bias or confounding was planned to be checked in sensitivity analyses by (i) including only meta-analyses with an arbitrary cut-off of at least 10 trials/meta-analysis, (ii) comparing the results of fixed-effect and random-effects models, and (iii) including only the largest meta-analysis from each included Intervention-Control comparison. Additionally, (iv) a post hoc sensitivity analysis by including the 50% of meta-analyses with most included trials was performed after identifying signs of small-study effects. Finally, (v) a sensitivity analysis was performed to account for different risk of bias for the randomization sequence generation or (vi) for the blinding of outcome measurement across trials by including both trial registration and bias as factors in the within-meta-analysis meta-regression of meta-analyses with at least 5 trials, before pooling the overall effect of trial registration across meta-analyses.

## **3. Results**

### *3.1. Study selection*

The literature search yielded a total of 1241 hits electronically and 18 hits manually as of September 2, 2017; 216 of which, proceeded to full text assessment after eliminating duplicates and ineligible studies by title or abstract (Figure 1; Supplementary Table 3a-3g). Finally, a total of 48 trials on similar comparisons were identified as eligible for inclusion in the present meta-epidemiological study. These were included in 16 separate meta-analyses on seven different topics, with some trial overlap

among meta-analyses. Four authors of identified studies were also contacted to request missing data (Supplementary Table 4), which were provided.

### *3.2. Study characteristics*

The 16 eligible meta-analyses included a total of 83 trials with overlap (median of 3.5 trials; interquartile range 3 to 6 trials; range 3 to 14 trials) and a total of 4988 randomized patients (median of 47 patients; interquartile range 30 to 60 patients; range 14 to 1000 patients). Analyzing the characteristics of included trials without overlap, a total of 59 published reports pertaining to 48 unique randomized trials were identified (Supplementary Table 5), which randomized a median of 40 patients (interquartile range 30 to 60 patients; range 14 to 1000 patients) to a total of 3188 patients. Among these 48 trials, only 10 of them (20.8%) had been registered in a trial registry overall, with registered trials within each meta-analysis ranging from 10% to 66% (Supplementary Table 6). A wide variety of outcomes were assessed in these trials including treatment duration, dental or skeletal treatment, and adverse effects like patient-reported pain or treatment-induced root resorption.

### *3.3. Risk of bias within studies*

Hints of bias (i.e. systematic differences in the results) within included trials was primarily addressed according to their registration status. Additionally, the adequacy of the random sequence generation was formally assessed according to the Cochrane risk of bias tool. From the 48 identified trials, low risk of bias was found for the randomization sequence in 32 trials (66.7%), while the rest of the trials had either unclear or high risk of bias. Adequate blinding of outcome assessment was found for 15 of the 48 (31.3%) identified trials. Registered trials were more likely to have low risk of bias for the randomization generation (90.0% vs 60.5%, respectively; relative risk: 1.49; 95% CI: 1.07 to 2.07) and more likely to have low risk of bias for blinding of outcome assessors (93.3% vs 54.6%; relative risk: 1.38; 95% CI: 0.56 to 3.43).

### *3.4. Results of individual meta-analyses and meta-epidemiological synthesis*

The results of all included meta-analyses including the registration status and risk of bias for randomization or blinding of outcome assessor can be seen in full detail in Supplementary Figure.

The meta-epidemiological synthesis of all 16 included meta-analyses indicated that considerable differences in the reported intervention effects were seen between registered and non-registered trials (pooled  $\Delta$ SMD: -0.36; 95% CI: -0.60, -0.12; P: 0.003). This indicated that registered trials reported less favorable intervention effects compared to non-registered trials, which could be interpreted as signs of bias. Based on Cohen's classification, this bias would be judged as of moderate magnitude. The observed absolute ( $\tau^2$ : 0; 95% CI: 0, 0.18) and relative heterogeneity ( $I^2$ : 0%; 95% CI: 0%, 42%) was minimal and the 95% predictive intervals coincided with the 95% CIs.

### 3.5. Additional analyses

No robust evidence could be found for differences among subgroups according to clinical scenario, outcome scope, nature, or direction (Table 1). Although great variation was seen (especially for the different clinical scenarios), very wide 95% CI were observed, indicating imprecision due to break-up of the sample.

As far as reporting biases are concerned, the funnel plot gave clear signs of asymmetry, which were formally confirmed by Egger's test (coefficient=-0.88; 95% CI=-1.59, -0.18; P=0.02). Based on the funnel plot the source of this asymmetry was taken to be small-study effects, with smaller and more imprecise meta-analyses reporting greater  $\Delta$ SMDs.

A number of pre-defined sensitivity analyses were performed on the main analysis (Table 2). Choice of statistical model or choice of only one meta-analysis per clinical scenario was not associated with the observed effects. Due to significant signs of small-study effects an additional *post hoc* sensitivity analysis with only the 50% largest meta-analyses was performed, which yielded identical  $\Delta$ SMD. Additionally, a separate sensitivity analysis controlling for low or unclear/high risk of bias for the generation of the randomization sequence found likewise that the observed effects were robust ( $\Delta$ SMDs of -0.36 and -0.37 for the original and adjusted analysis, respectively). Finally, a separate sensitivity analysis controlling for low or unclear/high risk of bias for blinding outcome assessment found that trial registration had considerably higher influence on the observed effects ( $\Delta$ SMDs of -0.36 and -1.80 for the original and adjusted analysis, respectively), but caution is needed as only 3 meta-analyses contributed to this.

## 4. Discussion

### 4.1. Principal findings

The present review summarizes empirical evidence up to September 2017 about the effects of trial registration on the results of orthodontic randomized clinical trials. Empirical evidence from 16 meta-analyses and 4–988 patients indicated that registered trials report considerably less beneficial treatment effects compared to non-registered trials, which can be interpreted as signs of bias of moderate magnitude. The fact that bias from lack of registration was found to be of moderate magnitude must not be underestimated, since this source of bias can act in an additive manner together with other known bias-related sources, such as; inadequate randomization or baseline imbalance, lack of blinding, small sample size, choice of control group, and others [19, 31-36].

### 4.2. Comparison with other studies

To our knowledge this is the first study to provide statistically significant empirical evidence of bias from lack of trial registration in an oral health field. The only study similar to ours is the comprehensive meta-epidemiological study from Dechartres et al. [8], who assessed Cochrane Reviews with binary outcomes published between 2011 and 2014. Although they included a greater number of meta-analyses ( $n=37$ ) across various medical fields, they found a small effect indicating that non-registered trials tended to show larger treatment effect estimates than registered trials (ratio of odds ratios=0.85; 95% CI=0.67-1.08), which was not statistically significant. Differences with our results could be explained by the inclusion in the Dechartres et al. [8] study of more heterogeneous trial outcomes than the present study, where only 'hard' outcomes were included. Additionally, Dechartres et al. [8] found similar magnitude of bias for non-registered versus registered trials (ratio of odds ratios of 0.85)—although not statistically significant. Another cross-sectional overview of randomized trials found only a weak association between trial registration and positive study results (adjusted risk ratio of 0.87) and a possible variation between non-industry and industry funded trials [10], but concluded that evidence is inconsistent. However, it must be noted that this was a large unselected group of randomized trials across various research question and unstratified by disease, intervention, and outcome and therefore, a potentially existing effect might have been masked by the pooled analysis.

#### 4.3. Strengths and limitations

Strengths of the current study include the *a priori* development of a research protocol that was precisely followed and the detailed reporting of all post hoc choices (Appendix), which supports the study's credibility [37]. Additionally, maximized data output through author communications, use of an improved variance estimator [21], graphical assessment of the effects' clinical relevance with contours of magnitude [38], and transparent open data provision [27] can be counted among the study's strengths.

This study also has some limitations. First, it was based on a convenience sample limited to a dental specialty field, which meant that only a small number of eligible trials could eventually be included and that the meta-epidemiological synthesis might be potentially underpowered. Therefore, additional empirical evidence is needed to confirm or refute the findings of the current study. Second, as only studies from a single field were included, the studies results might not directly transferable to other field, although no rationale for this exists. Third, trial registration might be associated with many other trial characteristics possibly linked to bias like geographic origin, number of study centers, sample size and used methods, which was not considered in this study. Finally, we did not differentiate between randomized trials having been prospectively or retrospectively registered and we did not directly assess firsthand discrepancies between the trials' published reports and protocols. These were not planned during protocol and it would not be possible to formally integrate those factors in the analysis, due to the already limited existing material. This can be the focus of future empirical studies with a wider scope.

#### 4.4. Conclusions and policy implications

It is evident from the results of this study that trial registration, apart from being crucial to the transparency and credibility of a trial, can potentially influence either directly or indirectly the current evidence base and therefore clinical recommendations. Our findings support the the initiatives of the World Health Organization, the International Committee of Medical Journal Editors towards, and other research regulatory authorities to provide a depository for trial registration and to promote policies that support trial registration and adherence to reporting guidelines. The current situation of clinical trials in orthodontics suboptimal both in terms of registration [15] and reporting quality [39]. Efforts have been made from orthodontic journals to improve author adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [40]. However and even though a large part of medical journals requires all

submitted trials to be registered [41], only five out of the ten existing orthodontic journals only mention trial registration in their author instructions, while only one (Journal of Orthodontics) words this explicitly as a requirement for publication [15]. It is important finally to note that trial registration does not preclude the use of inappropriate methods or bias.

#### *4.5. Summary*

The present meta-epidemiological study provides empirical evidence of bias originating from a lack of protocol registration among randomized clinical trials in orthodontics and dentofacial orthopaedics. Therefore, caution is warranted by the interpretation of unregistered trials or by their incorporation in systematic reviews and clinical guidelines. However, the evidence base that was used in the present study is limited and future studies are expected to expand upon it.

**Acknowledgements**

We thank Sophy K Barber (Leeds Dental Institute), Peter Miles (Caloundra, Queensland), Mueez Shedam (Rangoonwala Dental College and Research Centre), and Yanhua Xu (Kunming Medical University School) for providing details of their studies.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Data availability**

The datasets and commands of this study are openly available through Zenodo (<http://doi.org/10.5281/zenodo.1186318>).

## References

- [1] Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: [www.cochrane-handbook.org](http://www.cochrane-handbook.org). Accessed September 26th 2017.
- [2] De Angelis C, Drazen JM, Frizelle FA, et al. International Committee of Medical Journal Editors. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Lancet* 2004;356:911-2.
- [3] Dwan K, Altman DG, Cresswell L, Blundell M, Gamble CL, Williamson PR. Comparison of protocols and registry entries to published reports for randomised controlled trials. *Cochrane Database Syst Rev* 2011;1:MR000031.
- [4] Tramèr MR, Reynolds DJ, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. *BMJ* 1997;315:635-40.
- [5] Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. *Health Technol Assess* 2000;4:1-115.
- [6] Papageorgiou SN, Kloukos D, Petridis H, Pandis N. Publication of statistically significant research findings in prosthodontics & implant dentistry in the context of other dental specialties. *J Dent* 2015;43:1195-202.
- [7] Dechartres A, Trinquart L, Faber T, Ravaud P. Empirical evaluation of which trial characteristics are associated with treatment effect estimates. *J Clin Epidemiol* 2016;77:24-37.
- [8] Dechartres A, Ravaud P, Atal I, Riveros C, Boutron I. Association between trial registration and treatment effect estimates: a meta-epidemiological study. *BMC Med* 2016;14:100.
- [9] Emdin C, Oduyayo A, Hsiao A, et al. Association of cardiovascular trial registration with positive study findings: Epidemiological Study of Randomized Trials (ESORT). *JAMA Intern Med* 2014;356.
- [10] Oduyayo A, Emdin CA, Hsiao AJ, et al. Association between trial registration and positive study findings: cross sectional study (Epidemiological Study of Randomized Trials-ESORT). *BMJ* 2017;356:j917.



- [11] Lesaffre E, Garcia Zattera MJ, Redmond C, Huber H, Needleman I; ISCB Subcommittee on Dentistry. Reported methodological quality of split-mouth studies. *J Clin Periodontol* 2007;34:756–61.
- [12] Koletsi D, Pandis N, Polychronopoulou A, Eliades T. Does published orthodontic research account for clustering effects during statistical data analysis? *Eur J Orthod* 2012;34:287–92.
- [13] Ciani O, Buyse M, Garside R, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. *BMJ* 2013;346:f457.
- [14] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1–e34.
- [15] Papageorgiou SN, Antonoglou GN, Sándor GK, Eliades T. Randomized clinical trials in orthodontics are rarely registered a priori and often published late or not at all. *PLoS One* 2017;12:e0182785.
- [16] Papageorgiou SN, Konstantinidis I, Papadopoulou K, Jäger A, Bourauel C. Clinical effects of pre-adjusted edgewise orthodontic brackets: a systematic review and meta-analysis. *Eur J Orthod* 2014;36:350–63.
- [17] Papageorgiou SN, Götz L, Jäger A, Eliades T, Bourauel C. Lingual vs. labial fixed orthodontic appliances: systematic review and meta-analysis of treatment effects. *Eur J Oral Sci* 2016;124:105–18.
- [18] Saloom HF, Papageorgiou SN, Carpenter GH, Cobourne MT. Impact of obesity on orthodontic tooth movement in adolescents: a prospective clinical cohort study. *J Dent Res* 2017;96:547–54.
- [19] Papageorgiou SN, Antonoglou GN, Tsiranidou E, Jepsen S, Jäger A. Bias and small-study effects influence treatment effect estimates: a meta-epidemiological study in oral medicine. *J Clin Epidemiol* 2014;67:984–92.
- [20] Papageorgiou SN, Xavier GM, Cobourne MT. Basic study design influences the results of orthodontic clinical investigations. *J Clin Epidemiol* 2015;68:1512–22.
- [21] Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* 2016;7:55–79.

- [22] Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York: Academic Press; 1988.
- [23] Papageorgiou SN. Meta-analysis for orthodontists: Part II--Is all that glitters gold? *J Orthod* 2014;41:327–36.
- [24] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- [25] Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009;172:137–59.
- [26] IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016;6:e010247.
- [27] Papageorgiou SN, Xavier GM, Cobourne MT, Eliades T. Registered trials report less beneficial treatment effects than unregistered ones: a meta-epidemiological study in orthodontics [Data set]. Zenodo. <http://doi.org/10.5281/zenodo.1186318>.
- [28] Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract* 2008;14:951–7.
- [29] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [30] Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991–6.
- [31] Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. *Ann Intern Med* 2011;155:39–51.
- [32] Savović J, Jones H, Altman D, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technol Assess* 2012;16:1–82.
- [33] Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ* 2013;346:f2304.

- [34] Papageorgiou SN, Koretsi V, Jäger A. Bias from historical control groups used in orthodontic research: a meta-epidemiological study. *Eur J Orthod* 2017;39:98–105.
- [35] Wallach JD, Sullivan PG, Trepanowski JF, Steyerberg EW, Ioannidis JP. Sex based subgroup differences in randomized controlled trials: empirical evidence from Cochrane meta-analyses. *BMJ* 2016;355:i5826.
- [36] Papageorgiou SN, Höchli D, Eliades T. Outcomes of comprehensive fixed appliance orthodontic treatment: A systematic review with meta-analysis and methodological overview. *Korean J Orthod* 2017;47:401–413.
- [37] Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383:166–75.
- [38] Papageorgiou SN. Meta-analysis for orthodontists: Part II--Is all that glitters gold? *J Orthod* 2014;41:327–36.
- [39] Pandis N, Shamseer L, Kokich VG, Fleming PS, Moher D. Active implementation strategy of CONSORT adherence by a dental specialty journal improved randomized clinical trial reporting. *J Clin Epidemiol* 2014;67:1044–8.
- [40] Pandis N, Polychronopoulou A, Eliades T. An assessment of quality characteristics of randomised control trials published in dental journals. *J Dent* 2010;38:713–21.
- [41] Hopewell S, Altman DG, Moher D, Schulz KF. Endorsement of the CONSORT Statement by high impact factor medical journals: a survey of journal editors and journal 'Instructions to Authors'. *Trials* 2008;9:20.

## Figure Legends

**Fig. 1.** Flowdiagram for the identification and selection of studies in this meta-epidemiological study.

**Fig. 2.** Contour-enhanced forest plot for the meta-epidemiological synthesis using a Paule-Mandel random-effects model. Results are given as  $\Delta$ SMDs and their 95% CIs.  $\Delta$ SMD, standardized mean difference; CI, confidence intervals.

**Fig. 3.** Contour-enhanced funnel plot summarizing for the meta-epidemiological synthesis.  $\Delta$ SMD, standardized mean difference.

## Supplementary data

Supplementary data related to this article can be found at:

**Supplementary Table 1** List of identified registered, completed, and published trials in orthodontics (from PMID 28777820).

**Supplementary Table 2** Literature searches performed on 15 August 2017 for the identification of registered or unregistered trials and systematic reviews/meta-analyses thereof for each of the eligible fields.

**Supplementary Table 3a** List of included/excluded studies on the topic of self-ligating brackets.

**Supplementary Table 3b** List of included/excluded studies on the topic of vibration as adjunct.

**Supplementary Table 3c** List of included/excluded studies on the topic of piezocision.

**Supplementary Table 3d** List of included/excluded studies on the topic of maxillary protraction for maxillary deficiency.

**Supplementary Table 3e** List of included/excluded studies on the topic of skeletal anchorage for space closure.

**Supplementary Table 3f** List of included/excluded studies on the topic of gum as adjunct.

**Supplementary Table 3g** List of included/excluded studies on the topic of low level light therapy.

**Supplementary Table 4** Communications with trialists to request data.

**Supplementary Table 5** Characteristics of included trials.

**Supplementary Table 6** Details of included meta-analyses.

**Supplementary Figure** Forest plots for meta-analyses included in meta-epidemiological synthesis.

**Appendix** Post hoc changes to the protocol.

**Table 1.** Mixed-effects subgroup analyses of the meta-epidemiological synthesis. Negative effects indicate that registered trials show less beneficial treatment effects.

Factor	Category	Meta-analyses	$\Delta$ SMD (95% CI)	P*
Clinical scenario	Active vs passive self-ligating brackets for comprehensive treatment	1	-0.38 (-1.81,1.04)	0.39
	Maxillary protraction vs untreated control for maxillary deficiency	3	-0.96 (-1.66,-0.27)	
	Chewing gum vs no chewing gum for comprehensive treatment	1	-2.06 (-5.55,1.42)	
	Light therapy versus no light therapy for comprehensive treatment	1	-0.37 (-5.71,4.98)	
	Temporary anchorage devices vs conventional anchorage for anchorage reinforcement during extraction treatment	3	-0.56 (-1.40,0.29)	
	Self-ligating brackets vs conventional brackets for comprehensive treatment	6	-0.22 (-0.52,0.08)	
	Vibration adjuncts vs no vibration adjuncts for comprehensive treatment	1	-0.23 (-1.27,0.82)	
Outcome scope	Treatment efficacy	12	-0.51 (-0.83,-0.19)	0.11
	Adverse effects	4	-0.17 (-0.53,0.19)	
Outcome nature	Objective	13	-0.46 (-0.75,-0.17)	0.15
	Subjective (patient reported pain)	3	-0.14 (-0.56,0.29)	
Outcome direction <sup>a</sup>	Negative is favorable intervention effect	12	-0.29 (-0.59,-0.00)	0.40
	Positive is favorable intervention effect	4	-0.49 (-0.90,-0.07)	

*Abbreviations:*  $\Delta$ SMD, difference in standardized mean differences; CI, confidence interval.

<sup>a</sup> this pertains to initial direction of outcome. Outcomes were uniformly transformed on the same direction to pool.

\* for between-subgroup differences.

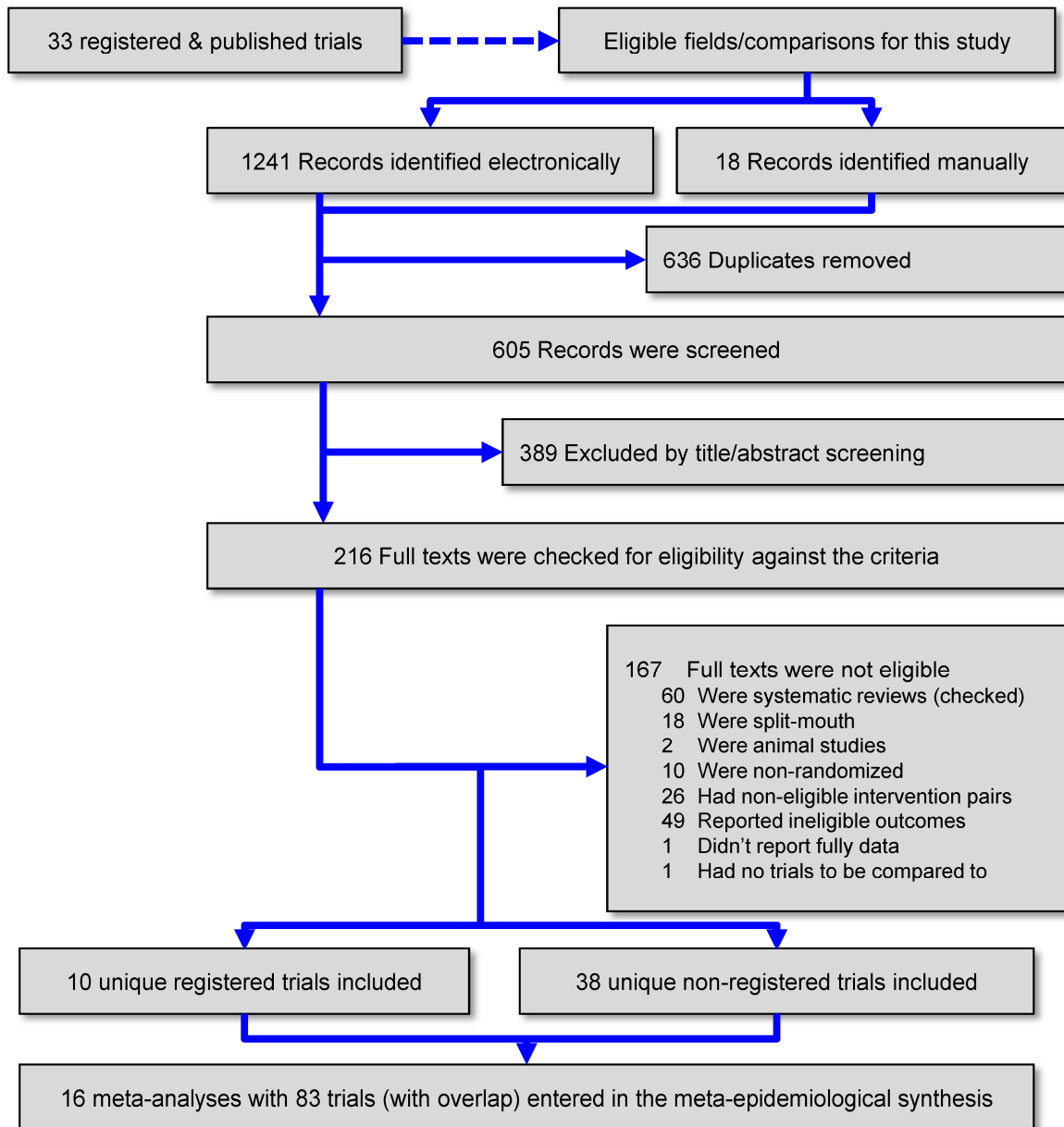
**Table 2.** Sensitivity analyses of the meta-epidemiological synthesis. Negative effects indicate that registered trials show less beneficial treatment effects.

Analysis	Meta-analyses	$\Delta$ SMD (95% CI)	P
Original analysis	16	-0.36 (-0.60,-0.12)	0.003
(i) Fixed effect model	16	Same as original	
(ii) Only the largest meta-analysis of each Intervention-Control comparison included	7	-0.30 (-0.63,0.02)	0.06
(iii) 50% of meta-analyses with most included trials	8	-0.36 (-0.71,-0.00)	0.05
(iv) Meta-analyses with $\geq 10$ included trials	2	-0.94 (-2.09,0.22)	0.11
(v) Analysis adjusted for risk of bias due to inadequate random sequence generation <sup>a</sup>	6	-0.37 (-0.79,0.05)	0.09
(vi) Analysis adjusted for risk of bias due to inadequate outcome blinding <sup>b</sup>	3	-1.80 (-3.54,-0.06)	0.04

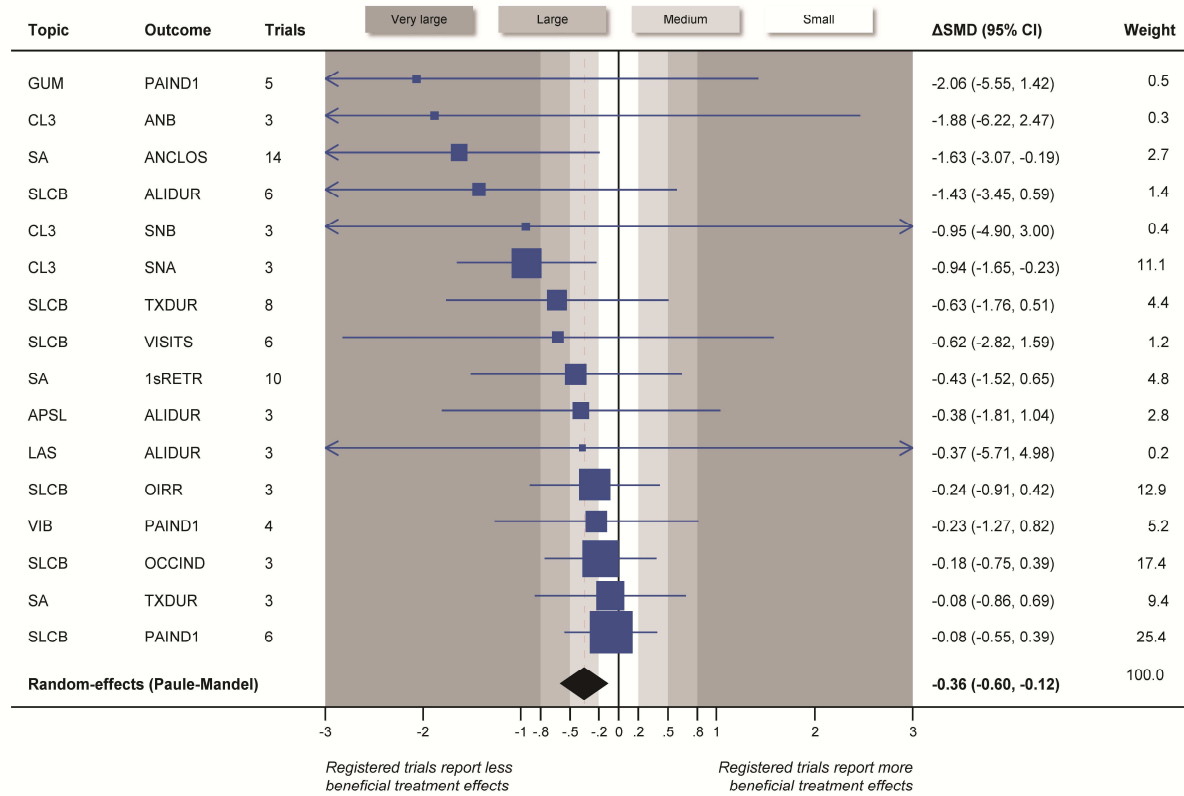
Abbreviations:  $\Delta$ SMD, difference in standardized mean differences; CI, confidence interval.

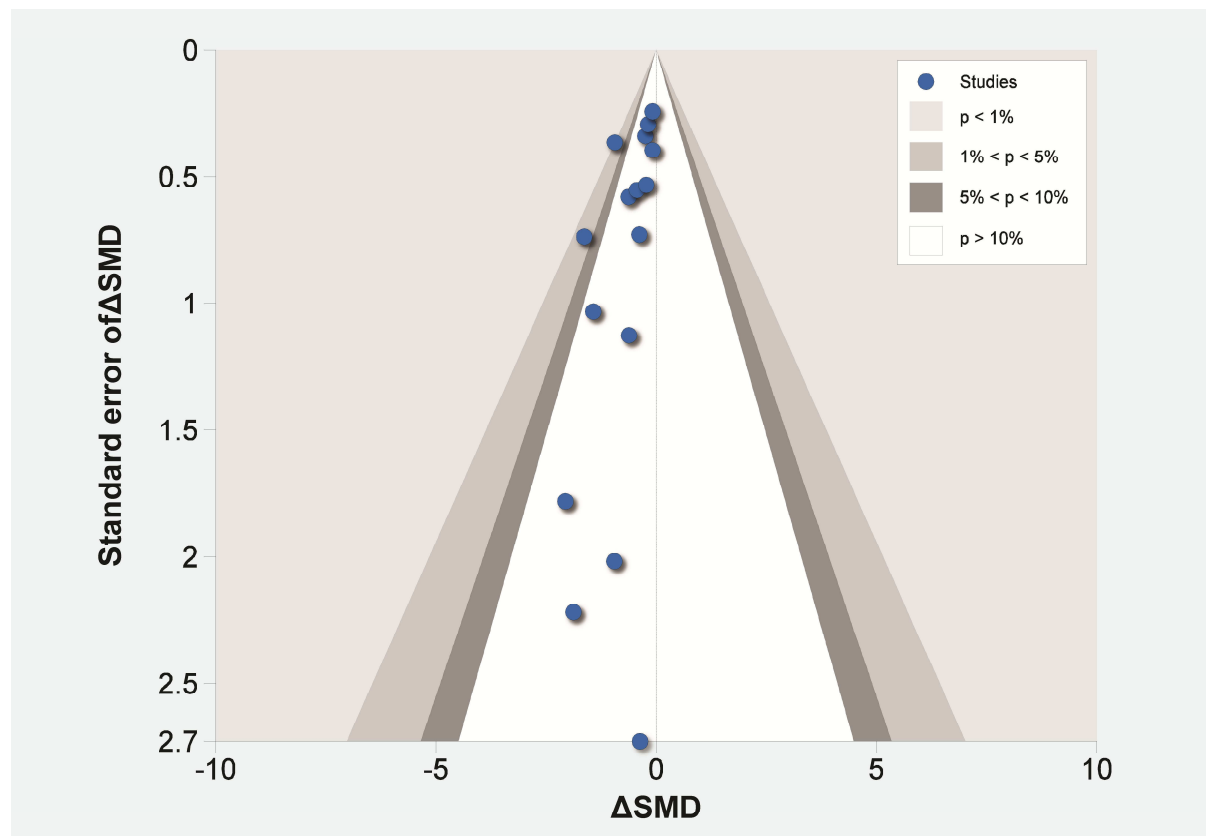
<sup>a</sup> Only meta-analyses with  $\geq 5$  trials were included in this. Both registration status and low (or unclear/high) risk of bias for random sequence generation were used within each meta-analysis to calculate  $\Delta$ SMDs, which were afterwards pooled across meta-analyses.

<sup>b</sup> Only meta-analyses with outcomes that could be blinded were included. Both registration status and low (or unclear/high) risk of bias for blind outcome measurement were used within each meta-analysis to calculate  $\Delta$ SMDs, which were afterwards pooled across meta-analyses.









# Registered trials report less beneficial treatment effects than unregistered ones: a meta-epidemiological study

## What is new?

### Key findings

- Registered randomized trials in orthodontics report less beneficial treatment effects than unregistered ones.
- The magnitude of bias from lack of trial registration was robust to small study effects and trial risk of bias.

### What this adds to what was known?

- ~~There appears to be a systematic difference in the results between randomised and non-randomised trials in orthodontics, with a trend for the former to report less beneficial treatment effects~~
- ~~These findings are highly relevant to the interpretation of existing biomedical literature and ongoing trial registration incentives from editors and research regulatory authorities.~~
- Empirical evidence indicates that various characteristics pertaining to the design and conduct of randomized trials lead to exaggerated effect estimates.
- It is believed that a priori trial registration can safeguard against reporting bias.
- This is to our knowledge the first study to definitely show empirical bias arising from non-registration of randomized trials.

### What is the implication and what should change now?

- Estimates coming from non-registered ~~randomized~~ randomized trials or meta-analyses thereof should be interpreted with caution.

**Registered trials report less beneficial treatment effects than unregistered ones: a meta-epidemiological study**

**Conflicts of interests**

None.